Online Supplement

Screening Methods

Based on at least two-view screen-film (n=4351) or digital (n=3122) mammography, visually estimated breast density was recorded as < 25%; 26 to 40%; 41 to 60%; 61 to 80%; or > 80% dense. All radiologist investigators met experience requirements and had completed qualification tasks as previously detailed.[7] Computer-assisted detection was not permitted. Ultrasound scanning was physician performed within two weeks of the mammogram (and usually the same day), with standardized technique and documentation,[7] using high-resolution linear array broad bandwidth transducers with maximum frequency of at least 12 MHz. Interpretive criteria for both mammography and ultrasound were standardized as well.[35] For 1.6% of analyzable participants, the first study screen was their first-ever (baseline) mammographic examination;[7] otherwise, prior breast imaging was available at the time of interpretation for all screens.

MR Technique

To minimize background parenchymal enhancement, MR examinations were scheduled within 7 to 14 days of onset of menses in premenopausal women when possible and prior to any biopsies prompted by screening mammography or ultrasound. Simultaneous bilateral contrast-enhanced breast MRI utilized dedicated breast coils on 1.5T systems. Axial or

sagittal T1 and fat-suppressed T2 or inversion recovery images were obtained prior to contrast injection. A three-dimensional spoiled gradient echo volume acquisition with fat suppression was obtained through both breasts both prior to and a minimum of three times following intravenous power injection of 0.1 mmol/kg Gd-DTPA, with entirety of both breasts imaged within 3 minutes, delayed imaging for minimum total of 6 minutes, and at least 3 post-contrast acquisitions through both breasts. In-plane voxel size was not greater than 1.0-mm x 1.0-mm x 3-mm slice thickness. Images were viewed with subtraction technique and maximum intensity projection technique. Prior to accruing MRI participants, sites submitted a deidentified sample contrast-enhanced MRI examination for review by Dr. R. Edward Hendrick for quality assurance and to adjust scanning parameters. Computer-assisted kinetic analysis could be performed.

Features and assessments of each lesion and by breast were recorded using BI-RADS.[14,36,37] To allow meaningful receiver operating characteristic (ROC) curve analysis, we did not allow use of BI-RADS 0, incomplete. Recommendations for routine annual imaging, short interval follow-up in 6 months, additional imaging, and/or biopsy, were recorded separately.

Additional Results

Time between Screens and Time to Perform US

Time between screening mammography rounds averaged 378 to 380 days (Table E1) and between 24-month

mammogram and protocol MRI, 22 days. Time to perform screening ultrasound decreased from 19 minutes at time 0 to

less than 15 minutes at time 24 months (Table E2).

Supplemental Yield of US after Digital Mammography

Across three years of screening, supplemental US provided significant detection benefit with both film and digital

mammography, with supplemental yield of 3.7 per 1000 (95%CI 2.1 to 5.5) for film and 5.1 per 1000 (95%CI 2.7 to 7.7) for

digital mammography (p<.001 each), and for all women less than age 50 (3.8 per 1000, 95%CI 1.4 to 6.5) or at least 50

years old (4.5 per 1000, 95%CI 2.8 to 6.1) (p=.003 and p<.001 vs. mammography alone, respectively).

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Table E1. Time between Screens (days)

	Year 1 mammo to year 2 mammo	Year 2 mammo to year 3 mammo	Year 3 mammo to protocol MRI
N	2490	2284	612
mean	380	378	25
SD	32	33.9	18.7
median	371	371	22
range	269-675	231-683	0-87

Table E2. Time to Perform Screening US (minutes)

	Year 1	Year 2	Year 3
N	2659	2493[a]	2321
mean	19.2	16.7	14.7
SD	11.9	10.4	9.2
median	17	15	13

	Year 1	Year 2	Year 3
range	1-144	1-166	1-121

[a] Three participants not included in year 1 analysis set were included in year 2.

Table 5A. **Results of Supplemental US Screening in Addition to Mammography for Women with and without Personal History of Breast Cancer (PHBC)**

		Mammography (M) alone			Combined Mammography and US (M + US)			Difference of (M + US) and M alone			Ultrasound (US) alone		
		Est	(No/ Total)	95% CI	Est	(No/ Total)	95% CI	Est	95% CI	pvalue	Est	(No/ Total)	95% CI
Yield, per 1000 (N/Total)	PHBC	8.2	(33/ 4010)	(5.7, 11.5)	12.5	(50/ 4010)	(9.3, 16.4)	4.2	(2.5, 6.2)	<0.001	8.7	(35/ 4010)	(6.1, 12.1)
	No PHBC	7.5	(26/ 3463)	(4.9, 11.0)	11.8	(41/ 3463)	(8.5, 16.0)	4.3	(2.3, 6.6)	<0.001	6.6	(23/ 3463)	(4.2, 9.9)
	Difference	0.7		(-3.3, 4.4)	0.6		(-4.4, 5.5)	-0.1	(-3.0, 2.9)	0.950	2.1		(-1.9, 5.9)
Sensitivity, % (N/Total)	PHBC	55.9	(33/ 59)	(42.4, 68.8)	84.7	(50/ 59)	(73.0, 92.8)	28.8	(18.6, 40.7)	<0.001	59.3	(35/ 59)	(45.7, 71.9)
	No PHBC	50.0	(26/ 52)	(35.8, 64.2)	78.8	(41/ 52)	(65.3, 88.9)	28.8	(17.3, 40.4)	<0.001	44.2	(23/ 52)	(30.5, 58.7)
	Difference	5.9		(-12.5, 24.6)	5.9		(-8.8, 20.0)	-0.0	(-15.9, 15.6)	0.997	15.1		(-2.4, 32.6)
Specificity, % (N/Total)	PHBC	91.4	(3611/ 3951)	(90.5, 92.3)	83.1	(3283/ 3951)	(81.9, 84.2)	-8.3	(-9.3, -7.4)	<0.001	88.2	(3485/ 3951)	(87.2, 89.2)
	No PHBC	89.4	(3051/ 3411)	(88.4, 90.5)	77.8	(2654/ 3411)	(76.4, 79.2)	-11.6	(-12.8, -10.4)	<0.001	84.0	(2865/ 3411)	(82.7, 85.2)
	Difference	1.9		(0.7, 3.3)	5.3		(3.5, 7.1)	3.3	(1.7, 4.9)	<0.001	4.2		(2.7, 5.7)
Recall Rate, % (N/Total)	PHBC	9.3	(373/ 4010)	(8.4, 10.2)	17.9	(718/ 4010)	(16.7, 19.1)	8.6	(7.7, 9.5)	<0.001	12.5	(501/ 4010)	(11.5, 13.6)
	No PHBC	11.1	(386/ 3463)	(10.1, 12.2)	23.0	(798/ 3463)	(21.6, 24.5)	11.9	(10.6, 13.1)	<0.001	16.4	(569/ 3463)	(15.2, 17.7)
	Difference	-1.8		(-3.2, -0.4)	-5.1		(-7.0, -3.4)	-3.3	(-4.9, -1.7)	<0.001	-3.9		(-5.6, -2.4)
PPV1,[b] % (N/Total)	PHBC	8.8	(33/ 373)	(6.2, 12.2)	7.0	(50/ 718)	(5.2, 9.1)	-1.9	(-3.5, -0.2)	0.026	7.0	(35/ 501)	(4.9, 9.6)
	No PHBC	6.7	(26/ 386)	(4.4, 9.7)	5.1	(41/ 798)	(3.7, 6.9)	-1.6	(-3.2, -0.0)	0.050	4.0	(23/ 569)	(2.6, 6.0)
	Difference	2.1		(-1.6, 5.8)	1.8		(-0.3, 4.2)	-0.3	(-2.6, 2.0)	0.808	2.9		(0.8, 6.6)
Short-term Follow-up Rate, % (N/Total)	PHBC	2.2	(90/ 4010)	(1.8, 2.8)	7.5	(300/ 4010)	(6.7, 8.3)	5.2	(4.5, 5.9)	<0.001	5.5	(220/ 4010)	(4.8, 6.2)
	No PHBC	2.0	(70/ 3463)	(1.6, 2.5)	9.4	(324/ 3463)	(8.4, 10.4)	7.3	(6.4, 8.2)	<0.001	7.7	(266/ 3463)	(6.8, 8.6)
	Difference	0.2		(-0.5, 0.9)	-1.9		(-3.1, -0.6)	-2.1	(-3.2, -1.0)	<0.001	-2.2		(-3.3, -1.0)

Biopsy Rate, % **(N/Total)**	PHBC	2.2	(87/ 4010)	(1.7, 2.7)	6.9	(275/ 4010)	(6.1, 7.7)	4.7	(4.0, 5.3)	<0.001	5.4	(215/ 4010)	(4.7, 6.1)
	No PHBC	2.2	(75/ 3463)	(1.7, 2.7)	9.7	(336/ 3463)	(8.7, 10.7)	7.5	(6.6, 8.4)	<0.001	8.2	(284/ 3463)	(7.3, 9.2)
	Difference	0.0		(-0.6, 0.7)	-2.8		(-4.2, -1.6)	-2.8	(-4.0, -1.8)	<0.001	-2.8		(-4.0, -1.7)
PPV3,[c] % **(N/Total)**	PHBC	36.8	(32/ 87)	(26.7, 47.8)	17.8	(49/ 275)	(13.5, 22.9)	-19.0	(-26.7, -11.7)	<0.001	15.3	(33/ 215)	(10.8, 20.9)
	No PHBC	32.0	(24/ 75)	(21.7, 43.8)	11.0	(37/ 336)	(7.9, 14.9)	-21.0	(-29.1, -13.1)	<0.001	6.7	(19/ 284)	(4.1, 10.3)
	Difference	4.8		(-8.8, 18.6)	6.8		(1.9, 12.2)	2.0	(-8.7, 12.8)	0.714	8.7		(3.7, 14.0)

[a] Yield is the cancer detection rate

[b] PPV1 is defined as the malignancy rate among women with a positive screening test (i.e. recalled from screening for further testing or short-interval follow-up).

[c] PPV3 is defined as the malignancy rate among women with a positive screening test who underwent biopsy of the same lesion.

11   **Table 5B. Results of Supplemental MRI Screening in Addition to Mammography for Women with and without Personal History of Breast**

	M	M+MRI	(M+MRI)-(M)	MRI

12   **Cancer (PHBC)**

13

		Est	N/Total	95% CI	Est	N/Total	95% CI	Est	95% CI	P	Est	N/Total	95% CI
Yield[a] per 1000	PHBC	7.3	2/275	(0.9, 26.0)	14.5	4/275	(4.0, 36.8)	7.3	(-6.4, 21.0)	0.500	10.9	3/275	(2.3, 31.5)
	No PHBC	8.9	3/337	(1.8, 25.8)	35.6	12/337	(18.5, 61.4)	26.7	(6.5, 46.9)	0.004	32.6	11/337	(16.4, 57.7)
	Difference	-1.6		(-15.7, 12.4)	-21.1		(-45.7, 3.5)	-19.4	(-40.0, 1.1)	0.063	-21.7		(-44.4, 0.9)
Sensitivity (%)	PHBC	50.0	2/4	(6.8, 93.2)	100.0	4/4	(39.8, 100.0)	50.0	(-24.0, 124.0)	0.500	75.0	3/4	(19.4, 99.4)
	No PHBC	25.0	3/12	(5.5, 57.2)	100.0	12/12	(73.5, 100.0)	75.0	(42.2, 107.8)	0.004	91.7	11/12	(61.5, 99.8)
	Difference	25.0		(-28.4, 78.4)	0.0		(0.0, 0.0)	-25.0	(-78.4, 28.4)	0.359	-16.7		(-63.3, 29.9)
Specificity (%)	PHBC	95.2	258/271	(91.9, 97.4)	78.6	213/271	(73.2, 83.3)	-16.6	(-21.4, -11.8)	<.001	81.5	221/271	(76.4, 86.0)
	No PHBC	89.5	291/325	(85.7, 92.6)	64.0	208/325	(58.5, 69.2)	-25.5	(-30.6, -20.5)	<.001	70.8	230/325	(65.5, 75.7)
	Difference	5.7		(1.5, 9.8)	14.6		(7.4, 21.8)	8.9	(2.4, 15.5)	0.008	10.8		(3.9, 17.6)
PPV1[b] (%)	PHBC	13.3	2/15	(1.7, 40.5)	6.5	4/62	(1.8, 15.7)	-6.9	(-22.0, 4.8)	0.337	5.7	3/53	(1.2, 15.7)
	No PHBC	8.1	3/37	(1.7, 21.9)	9.3	12/129	(4.9, 15.7)	1.2	(-6.1, 8.3)	0.750	10.4	11/106	(5.3, 17.8)
	Difference	5.2		(-14.3, 24.8)	-2.9		(-10.7, 5.0)	-8.1	(-24.2, 8.1)	0.327	-4.7		(-13.1, 3.7)
Recall (%)	PHBC	5.5	15/275	(3.1, 8.8)	22.5	62/275	(17.7, 27.9)	17.1	(12.3, 21.9)	<.001	19.3	53/275	(14.8, 24.4)
	No PHBC	11.0	37/337	(7.8, 14.8)	38.3	129/337	(33.1, 43.7)	27.3	(22.2, 32.4)	<.001	31.5	106/337	(26.5, 36.7)
	Difference	-5.5		(-9.7, -1.4)	-15.7		(-22.9, -8.5)	-10.2	(-16.8, -3.7)	0.002	-12.2		(-19.2, -5.2)
Short-term Follow-up Rate (%)	PHBC	0.4	1/275	(0.0, 2.0)	14.2	39/275	(10.3, 18.9)	13.8	(9.4, 18.3)	<.001	13.8	38/275	(10.0, 18.5)
	No PHBC	0.6	2/337	(0.1, 2.1)	18.1	61/337	(14.1, 22.6)	17.5	(13.2, 21.9)	<.001	17.5	59/337	(13.6, 22.0)
	Difference	-0.2		(-1.3, 0.9)	-3.9		(-9.9, 2.0)	-3.7	(-9.6, 2.2)	0.219	-3.7		(-9.6, 2.2)
Biopsy Rate (%)	PHBC	1.5	4/275	(0.4, 3.7)	5.5	15/275	(3.1, 8.8)	4.0	(1.3, 6.7)	<.001	4.0	11/275	(2.0, 7.0)
	No PHBC	1.8	6/337	(0.7, 3.8)	13.1	44/337	(9.6, 17.1)	11.3	(7.6, 14.9)	<.001	12.2	41/337	(8.9, 16.1)

	Difference	-0.3		(-2.3, 1.6)	-7.6		(-12.2, -3.0)	-7.3	(-11.4, -3.1)	<.001	-8.2		(-12.4, -3.9)
PPV3 [c] **(%)**	**PHBC**	50.0	2/4	(6.8, 93.2)	26.7	4/15	(7.8, 55.1)	-23.3	(-66.7, 20.0)	0.251	18.2	2/11	(2.3, 51.8)
	No PHBC	50.0	3/6	(11.8, 88.2)	25.0	11/44	(13.2, 40.3)	-25.0	(-58.3, 10.6)	0.166	24.4	10/41	(12.4, 40.3)
	Difference	0.0		(-63.4, 63.4)	1.7		(-22.5, 25.8)	1.7	(-51.9, 55.2)	0.951	-6.2		(-31.5, 19.1)

[a] Yield is the cancer detection rate

[b] PPV1 is defined as the malignancy rate among women with a positive screening test (i.e. recalled from screening for further testing or short-interval follow-up).

[c] PPV3 is defined as the malignancy rate among women with a positive screening test who underwent biopsy of the same lesion.